IN THE CLAIMS

1. (PRESENTLY CANCELLED).

2. (CURRENTLY AMENDED) ~~The method according to claim 1~~ A method for producing one or more biocatalysts or a combinatorial array of biocatalysts comprising the step of:

a) providing a host cell;

b) recombining at least two biotransformation genes encoding proteins for modifying a chemical substrate into the host cell;

c) thereby producing at least one recombinant strain comprising a biocatalyst, wherein said at least two biotransformation genes introduce two different chemical functional groups, at least one of the at least two different chemical functional groups for catalyzing processes for selected from the group selected from forming carbon to carbon bonds, hydroxylation, halogenation, cycloaddition, and amination.

3. (CURRENTLY AMENDED) The method according to claim 2 ~~1~~ wherein said at least two biotransformation genes modify functional groups according to reactions selected from the group selected of

i. reduction;
ii. oxidation;
iii. hydrolysis;
iv. replacement;
v. ring cyclization;
vi. isomerization;
vii. epimerization; and
viii. dealkylation.

4. (CURRENTLY AMENDED) The method according to claim 3 wherein the reactions are selected from the group consisting of:

i. reduction of carboxylic acids, aldehydes, and ketones;
ii. oxidation of alcohols, sulfites, amino groups, and thiols;

iii. hydrolysis of nitriles;

iv. replacement of amino groups with hydroxyl groups.;

5. (PRESENTLY AMENDMENT) The method according to claim 2 ~~1~~ wherein said biotransformation genes provide functional group addition of groups capable of providing catalysis for processes selected from the group consisting of acylation, glycosylation, amidation, phosphorylation, and alkyl transfer.

6. (PRESENTLY AMENDED) The method according to claim 2 ~~1~~ wherein said biotransformation genes are derived from whole cells endowed with biotransformation ability as a result of genetic recombination and *in vivo* expression from one or both of constitutive promoter(s) and inducible promoter(s) to create whole-cell biocatalysts.

7. (ORIGINAL) The method according to claim 2 wherein said biotransformation genes are derived from whole cells endowed with biotransformation ability as a result of genetic recombination and *in vivo* expression from one or both of constitutive promoter(s) and inducible promoter(s) to create whole-cell biocatalysts.

8. (ORIGINAL) The method according to claim 3 wherein said biotransformation genes are derived from whole cells endowed with biotransformation ability as a result of genetic recombination and *in vivo* expression from one or both of constitutive promoter(s) and inducible promoter(s) to create whole-cell biocatalysts.

9. (ORIGINAL) The method according to claim 4 wherein said biotransformation genes are derived from whole cells endowed with biotransformation ability as a result of genetic recombination and *in vivo* expression from one or both of constitutive promoter(s) and inducible promoter(s) to create whole-cell biocatalysts.

10. (PREVIOUSLY CANCELLED)

11. (PREVIOUSLY CANCELLED)

12. (PREVIOUSLY CANCELLED)

13. (PREVIOUSLY CANCELLED)

14. (PREVIOUSLY CANCELLED)

15. (PREVIOUSLY CANCELLED)

16. (PREVIOUSLY CANCELLED)

17. (PRESENTLY AMENDED) A method for producing a combinatorial array of biocatalysts comprising the steps of:

a) providing a host cell;

b) recombining one biotransformation gene encoding protein for modifying a chemical substrate into the host cell;

c) thereby producing at least one recombinant strain comprising a biocatalyst;

d) then inserting the at least one recombinant strain comprising a biocatalyst into at least two sections of an array of biocatalysts.

18. (ORIGINAL) The method according to claim 17 wherein said at least one biotransformation gene introduces a chemical functional group selected from the group selected from carbon to carbon bonds, hydroxylation, halogenation, cycloaddition, and amination.

19. (PREVIOUSLY ADDED) A method for producing one biocatalyst comprising the step of:

a) providing a host cell of *Streptomyces lividans*;

b) recombining at least three biotransformation genes for modifying a chemical substrate into the host cell, the biotransformation genes being gene 1 replacement desVII, gene 2 replacement pikC, and gene 3 replacement desR;

c) thereby producing at least one recombinant strain comprising a biocatalyst providing three different chemical functional groups, at least one of the at least two chemical functional groups being able to modify functional groups according to a hydrolysis reaction one of said three biotransformation genes provide functional group addition of groups capable of providing catalysis for glycosylation, hydroxylation and glucolysation.

ISSUES IN THE OFFICE ACTION

Claim 4 has been Objected to as it is missing a period at the end of the claim.

Claim 4 has been amended to remove this issue.

Claim 1 has been Objected to As Containing an Improper Plural Term

Claim 1 is asserted to lack correspondence within the terms "comprising a biocatlysts" and should be corrected.

Claims 1-9 and 17-19 have been rejected under 35 USC 112, first paragraph as containing subject matter not reasonably conveyed to one skilled in the art as within the possession of the inventor at the time the Application was filed.

Claims 1-9 and 17-19 have been rejected under 35 USC 112, first paragraph as containing subject matter not enabled for the scope of the claims recited.

Claims 1-9 and 17-19 have been rejected under 35 USC 112, second paragraph as failing to distinctly claim and particularly point out that subject matter regarded as invention.

1. In claim 1, the term "biocatalyst is thought to be indefinite.
2. In claim 2, the limitation of "the at least two functional groups" is asserted to lack antecedent basis.
3. In claim 2, the Markush listing is asserted to be indefinite as the terms "hydroxylation" and "hydrogenation" are not chemical groups.
4. In claim 3, there is a lack of antecedent basis for the use of the terminology "said biotransformation genes" without prior recital.
5. In claims 5-8, the term "biotransformation genes" causes indeterminate metes and bounds for the scope of the claims.

Claims 1-9 have been rejected under 35 USC 102(b) as anticipated by Xue et al. (PNAS, October 12, 1999, 96(21), 11740-11745)

It is asserted that each and every limitation claimed is disclosed in the Xue et al. published article, which was available more than one year prior to the filing of the Application.

Claims 1-3 and 5-8 have been rejected under 35 USC 102(b) as anticipated by Stachelhaus et al. (**SCIENCE**, July 1995, 269, 69-72).

It is asserted that each and every limitation claimed is disclosed in the Stachelhaus et al. published article, which was available more than one year prior to the filing of the Application.

Claims 1-9 have been rejected under 35 USC 102(b) as anticipated by Albrecht et al. (*Journal of Biotechnology*, 1997, 58, 177).

It is asserted that each and every limitation claimed is disclosed in the Albrecht et al. published article, which was available more than one year prior to the filing of the Application.

Claims 1-9 and 17-19 have been rejected under 35 USC 102(e) as anticipated by Katz et al. (US Published Application 2002/-111317 A1, filed 24 September 2001).

APPLICANTS' RESPONSE

Claim 4 has been Objected to as it is missing a period at the end of the claim.

That error was corrected.

Claim 1 has been Objected to.

Claim 1 is asserted to lack correspondence within the terms "comprising a biocatlysts" and should be corrected.

This editorial error was corrected in the Amendment filed on June 4 2003. The issue is moot and has previously been removed.

Claims 1-9 and 17-19 have been rejected under 35 USC 112, first paragraph as containing subject matter not reasonably conveyed to one skilled in the art as within the possession of the inventor at the time the Application was filed.

This rejection is both legally and factually in error. The style of the rejection is strongly reminiscent of the rejections that were standard fair during the 1960's in which organic synthetic processes and generic claims to compounds were summarily dismissed as lacking enablement for the "millions of compounds" or, in the case of this rejection, "an infinite number of recombinant host cells." As noted in the following citation of case law, those rejections were overwhelmingly rejected as fundamentally lacking support in the law and for lacking proper analysis of the issues within the rejection.

It is to be first noted on a factual level that the term "biocatalyst," which the rejection repeatedly places in brackets to denote its lack of apparent meaning, shows up in 627 U.S. Patents issued as of 17 November 2003 and since 1976. This shows a substantial and common use of the term by those skilled in the art. 6,638,758 (the term appears in the Abstract and claim 1); 6,642,020 (claim 11); 6,638,419 (claims 4, 5 and 6); 6,620,602 (Title); 6,613,552 (Title); 6,605,452 (Field of the Invention); 6,600,077 (Title); and 6,560,921 (Title, Abstract, and claims 1-5 and 6). It is absolutely clear that those skilled in the art commonly use the term with a facile understanding of its scope and meaning. In fact, the vast majority of the more recent issued patents do not even bother to define the term. The description provided in the present specification is far more substantive than most of the patents cited above where the term is used in a clearly common meaning to those skilled in the art. It is first clear that the term itself has a

well understood meaning in the art and that such materials and their use are extensively understood by those skilled in the art.

It is to be further noted that the rejection has failed to provide sufficient reasoning as to why the specification does not provide a disclosure commensurate with the requirements of 35 USC 112, first paragraph (written description), but solely relies upon the assumed breadth of the claims as reason in itself for the lack of capability of the specification to support such breadth. As mentioned above, this entire line of attack on specifications and disclosure has been repeatedly denied by the courts:

> "If the Examiner and/or the Board intended a rejection under the first paragraph of section 112, it must be reversed inasmuch as the specification contains a statement {*read*, "written description] which is as broad as Appellant's broadest claims...both the Examiner and the Board seem to have taken the position that in order to 'justify,' as the Examiner said, or to 'support,' as the Board said, broad generic language in a claim, the specification must be equally broad I its naming and use of examples of representative compounds encompassed by the claim language. This position, however, misapprehends the proper function of such disclosure." (*In re Robins*, 166 USPQ 552, 555 (US Dist Ct. DC 1970).

> "Nor will we sustain the rejections under 35 USC 112 [first paragraph]. The objected to expressions may veryt well be broad, but the same or substantially the same expressions appear in the disclosure and are exemplified by several representative materials. [*Note*, no used in examples, but described] In the absence of reasons why these expressions would include materials inoperative for the appellant's purposes, the representation set forth in the specification of materials included within these broad expressions are here deemed adequate." (*Ex parte Laiderman*, PTO Bd. P.A. 175 USPQ 758 1971)

> "To comply with the description requirements it is not necessary that the application describe the claimed invention *in ipsis verbis*...; all that is required is that it reasonably convey to persons skilled in the art that, as of ghe filing date thereof, the inventor had possession of the subject matter later claimed by

> him...In the context of the present case, this translates into whether the parent application provides adequate direction which reasonably leads persons skilled in the art to the later claimed compound." (*In re Edwards, Rice and Soulen*, 196 USPQ 465, CCPA 1975)

There are other closely related cases with respect to the obligations of and burden on the Patent Office in presenting rejections on these grounds and the related grounds of enablement under 35 USC 112, first paragraph. These cases will be cited in the discussions of the other issues, but the underlying theme of the decisions and the failure to meet their requirements can be summarized as follows. The initial burden is on the Patent and Trademark Office to show why, based on scientific reasoning and principles, that the specification actually fails to meet the requirements of 35 USC 112, first paragraph, without mere accusation of breadth or the number of included compounds. That has not been done in the present rejection. Quite the opposite, the rejection repeatedly refers to the numbers and scope of the claims, without any technical reference to the technical failure of the specification in the written description (or later enablement) of specific compounds.

The rejection clearly fails to meet the minimum required standards for establishing an issue under this provision of Title 35. The rejection is in error and must be withdrawn.

Claims 1-9 and 17-19 have been rejected under 35 USC 112, first paragraph as containing subject matter not enabled for the scope of the claims recited.

Again, the rejection asserts that in view of the scope of the claims, the specification cannot have enabled such a scope with the limited disclosure provided. That rejection fails to meet the most minimum legal requirements for establishing an enablement issue under 35 USC 112, first paragraph.

> "Recitation of generic term 'polyethyleneamine' must be taken as assertion by applicants that all of the 'considerable number of compounds' which are included within the generic term, would, as a class, be operative to produce asserted enhancement of adhesion characteristics; Patent Office has no concern over breadth of term; its only relevant concern should be over truth of such assertion; first paragraph of 35 USC 112 requires nothing more than objective enablement;

how such as teaching is set forth, either by way of illustrative examples or by broad terminology, is of no importance.: *In re Marzocchi and Horton*, 169 USPQ 367, CCPA 1971).

Certain language in this decision is extremely material to the underlying failing of this rejection. The case law has clearly established that:

a) first paragraph of 35 USC 112 requires nothing more than objective enablement;

b) how such as teaching is set forth, either by way of illustrative examples or by broad terminology, is of no importance.

The entire underpinning of the rejection set forth in the Office Action is an attack on the breadth of the claims, the sparse number of the examples, and other factors that are not material to the underlying nature of the requirements of the statute as defined by case law. The rejection fails to establish even a *prima facie* case of lack of enablement under the standards required. The rejection is fundamentally in error and must be withdrawn.

Claims 1-9 and 17-19 have been rejected under 35 USC 112, second paragraph as failing to distinctly claim and particularly point out that subject matter regarded as invention.

1. In claim 1, the term "biocatalyst is thought to be indefinite."

As noted above, the term biocatalyst is found in 627 separate US Patents as of 17 November 2003. The term has an established and clear meaning to those of ordinary skill in the art. The rejection is clearly in error. The functional nature of the class of materials are well known in the art. Further definition, beyond the clear definition in the specification that is consistent with standard usage in the art, is not needed. (cf. *Ex parte Olson*, 173 USPQ 808, PTO Bd. App. and Int. 1971).

2. In claim 2, the limitation of "the at least two functional groups" is asserted to lack antecedent basis.

This claim has been amended in the manner suggested by the examiner. This issue has been removed.

3. In claim 2, the Markush listing is asserted to be indefinite as the terms "hydroxylation" and "hydrogenation" are not chemical groups.

Claim 2 has been amended to place the group of process functions into a parallel Markush Group. This issue has been overcome by amendment to the claims.

4. In claim 3, there is a lack of antecedent basis for the use of the terminology "said biotransformation genes" without prior recital.

This claim has been amended in the manner suggested by the Examiner. This issue has been removed by the amendment.

5. In claims 5-8, the term "biotransformation genes" and their recited process functions causes indeterminate metes and bounds for the scope of the claims.

Because of the nature of the function provided and its well understood basis of performance in the art (biocatalyzation, enzymatic activity, etc.), and the specific reactions that are described, one of ordinary skill in the art would be able to appreciate and provide specific catalytic groups for these processes. It must be remembered with respect to the scope of the invention that, contrary to the assertions of the Examiner, the predictability of the synthesis of the compounds and the nature of their performance is quite high. The invention is not a synthesis of completely new and original atom-by-atom groups, but rather is the addition of known groups together in a format that structurally supports each segment. The underlying bacteria provides a platform for carrying known biocatalytic groups. The groups are bound to the bacterial cell and merely carried in a manner that allows them to provide their known activity. In complexity, once the platform has been determined and the objective of attaching multiple enzymatic (e.g., biocatalytic) groups onto that platform has been conceived (an element of the present invention), all that needs to be dome is to use known procedures for attaching groups are used to attach those biocatalytic groups to the chosen cell. This is akin to originally conceiving that multiple sensing functions can be provided without interactive interference on a microcatheter and then physically attaching the various functions onto the microcatheter. Among the critical steps (but not the exclusive critical steps) in this invention is the determination that multiple catalytic functions can be carried on a single cell, that the individual different catalytic functions will be able to perform without interference, and then attaching the

biocatalytic functionalities 9e.g., enzymes) to the cell. The easiest technical step, once the contemplation of the invention has been achieved, is the physical (actually chemical) connection of the biocatalyst groups onto the cell. One skilled in the art, given the concept of attaching groups of specific functionality to a cell would be readily able to provide multiple mechanisms for such attachment, with bridging groups, biotinylation groups, or other functionalities non-destructively added to one end of the catalyst top be used to bind to the cell.

The rejection is clearly in error and must be withdrawn.

Claims 1-9 have been rejected under 35 USC 102(b) as anticipated by Xue et al. (PNAS, October 12, 1999, 96(21), 11740-11745)

It is asserted that each and every limitation claimed is disclosed in the Xue et al. published article, which was available more than one year prior to the filing of the Application. The rejection is in error as the reference fails to show a teaching of the essential and critical element recited in each claim in this application, namely:

In claim 2: "thereby producing at least one recombinant strain comprising a biocatalyst, wherein said at least two biotransformation genes introduce two different chemical functional groups, at least one of the at least two different chemical functional groups for catalyzing processes for selected from the group selected from forming carbon to carbon bonds, hydroxylation, halogenation, cycloaddition, and amination."

In claim 19: "...thereby producing at least one recombinant strain comprising a biocatalyst providing three different chemical functional groups, at least one of the at least two chemical functional groups being able to modify functional groups according to a hydrolysis reaction one of said three biotransformation genes provide functional group addition of groups capable of providing catalysis for glycosylation, hydroxylation and thereby producing at least one recombinant strain comprising a biocatalyst providing three different chemical functional groups, at least one of the at least two chemical functional groups being able to modify functional groups according to a hydrolysis reaction one of said three

biotransformation genes provide functional group addition of groups capable of providing catalysis for glycosylation, hydroxylation and glucolysation."

It is to be noted that there is no specific teaching of these limitations of adding different biocatalyst functions onto the same substrate as recited in these claims. The rejection presents general language, using a disclosure that happens to use plural terms in the descriptions, without any specific disclosure of the use of multiple and different biocatalyst groups. The rejection is based upon suppositions and hypotheses, not upon actual teachings in the reference. The rejection is fundamentally in error.

It is also to be noted that the rejection undercuts the basis for the rejection under 35 USC 112, first paragraph. The Examiner asserts that this reference (and the other references cited under 35 USC 102) teaches that it is obvious (and therefore enabled) to add multiple groups onto the described substrate. The teaching of the reference cannot be held in two distinct lights, one asserting that it enables practice of the invention, and then ignored as showing that the background art in combination with the specification fails to provide enablement for what is claimed. Rather, the art and the specification should be viewed as establishing that the claimed invention represents a new concept, the combination of multiple biocatalytic functions onto a single substrate, and the process needed to perform this task is shown and enabled in the specification, and further enabled by the background knowledge in the art (such as that cited erroneously under 35 USC 102).

The rejection is in error and should be withdrawn.

Claims 1-3 and 5-8 have been rejected under 35 USC 102(b) as anticipated by Stachelhaus et al. (SCIENCE, July 1995, 269, 69-72).

It is asserted that each and every limitation claimed is disclosed in the Stachelhaus et al. published article, which was available more than one year prior to the filing of the Application.

It is to be noted that there is no specific teaching of these limitations of adding different biocatalyst functions onto the same substrate as recited in these claims. The rejection presents general language, using a disclosure that happens to use plural terms in the descriptions, without any specific disclosure of the use of multiple and different biocatalyst

groups. The rejection is based upon suppositions and hypotheses, not upon actual teachings in the reference. The rejection is fundamentally in error.

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claimed. Rather, the art and the specification should be viewed as establishing that the claimed invention represents a new concept, the combination of multiple biocatalytic functions onto a single substrate, and the process needed to perform this task is shown and enabled in the specification, and further enabled by the background knowledge in the art (such as that cited erroneously under 35 USC 102).

The rejection is in error and should be withdrawn.

Claims 1-9 and 17-19 have been rejected under 35 USC 102(e) as anticipated by Katz et al. (US Published Application 2002/-111317 A1, filed 24 September 2001).

It is to be noted that there is no specific teaching of these limitations of adding different biocatalyst functions onto the same substrate as recited in these claims. The rejection presents general language, using a disclosure that happens to use plural terms in the descriptions, without any specific disclosure of the use of multiple and different biocatalyst groups. The rejection is based upon suppositions and hypotheses, not upon actual teachings in the reference. The rejection is fundamentally in error.

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The rejection is in error and should be withdrawn.

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